GPCO
unicancer
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STRASBOURG
Hôpital Hautepierre

XIX^ES JOURNÉES
DU GROUPE DE PHARMACOLOGIE CLINIQUE ONCOLOGIQUE

Alimentation en immunothérapie par anti PD1/PD-L1

Professeur Francois Ghiringhelli Dijon

Professeur Christos Chouaid Creteil

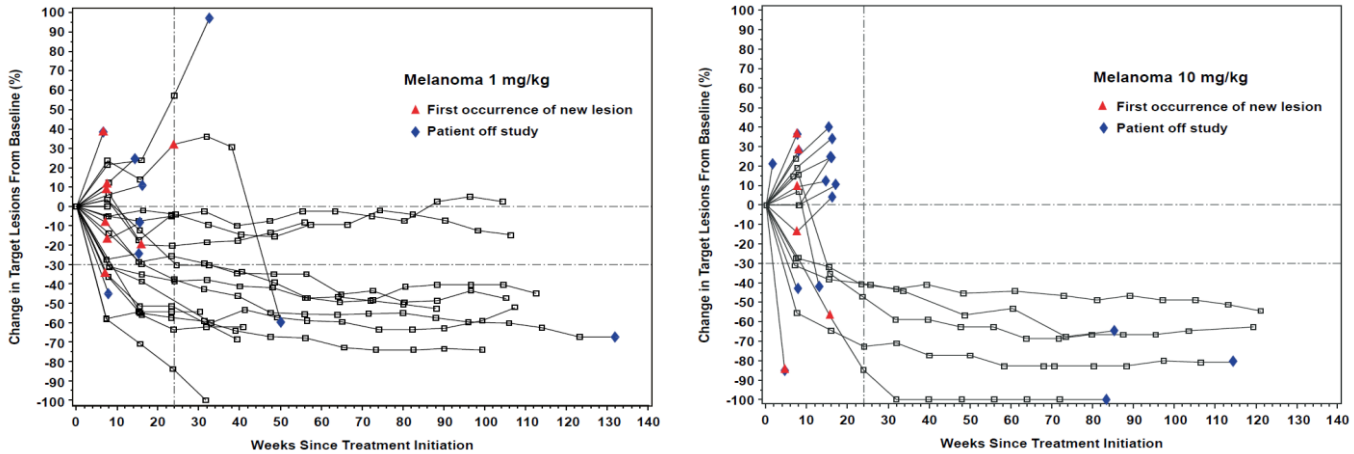
Lien d’intéret

Compagnie pharma	**Relation**
Amgen, MSD, Roche, Servier	congrès
Roche, MSD, Merck Serono, Brenus, Engetix, Odimma,	Consulting
Astra-Zeneca, Roche Genetech, Amgen, Xbiotech, Springwork	Financement de la recherche

Un peu de pharmacologie des anti PD1/PDL1

- Dans les études de phase I:
- Absence de preuve d'une relation dose-réponse, tout en montrant une biodisponibilité prolongée .

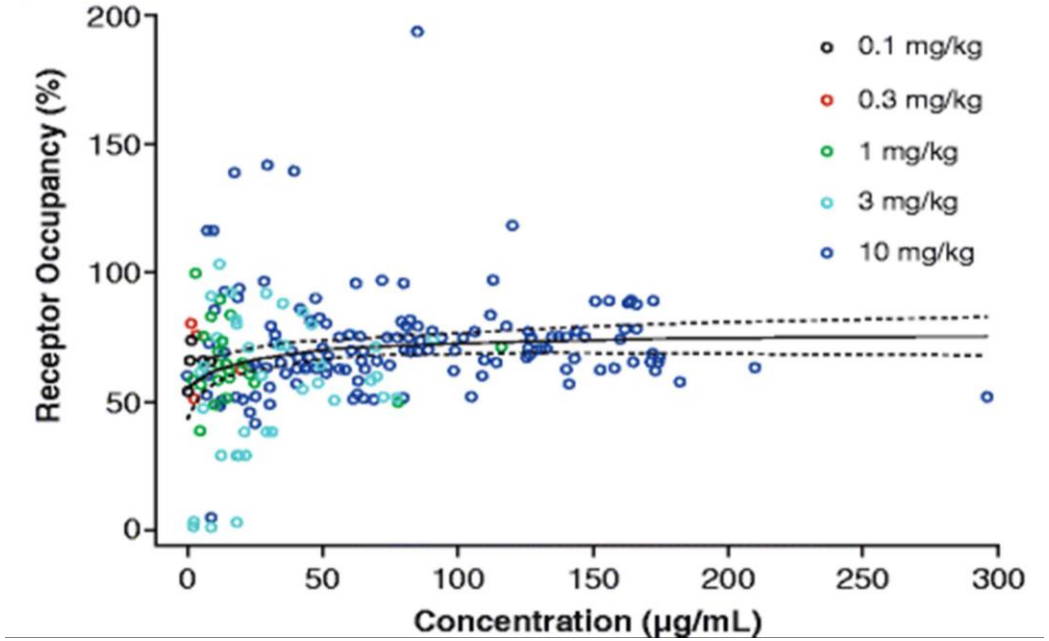
- Pour le pembrolizumab inhibition de la cible à des doses de 1 mg kg $^{-1}$ toutes les 3 semaines
- Pas de différence en survie entre 2 et 10mg/kg



Topalian SL et al. N Engl J Med 2012;366:2443-2454.

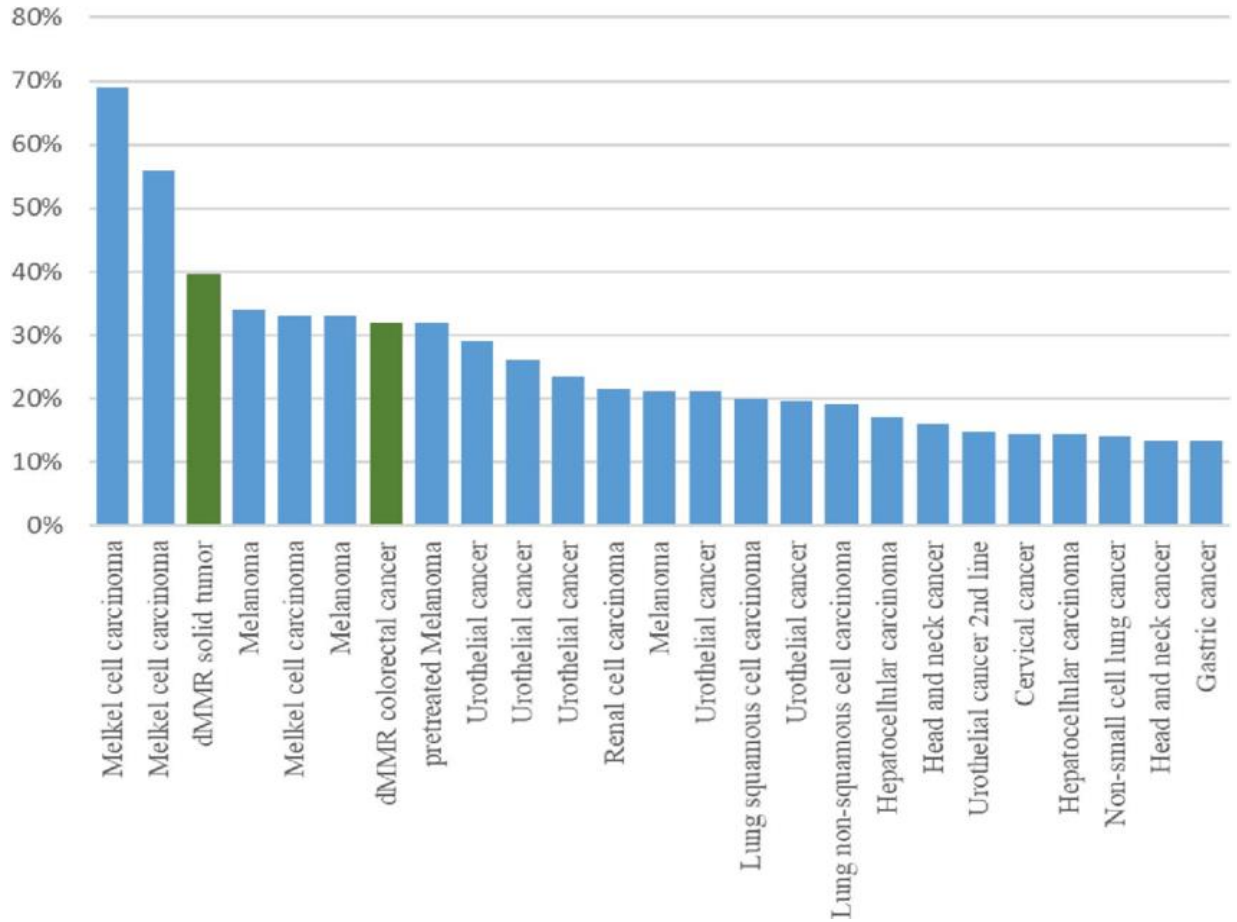
Un peu de pharmacologie des anti PD1/PDL1

- Dans les études de phase I:
- Pour le nivolumab pas de différences dose réponse ou liaison a la cible entre 0,1 et 10 mg·kg $^{-1}$ toutes les 2 semaines.
- La dose recommandée pour la phase 2 était de 3 mg kg $^{-1}$ toutes les 3 semaines = 15 fois la dose minimale efficace



Agrawal, S.,J. *Immunother. Cancer* **4**, 72 (2016)

Optimisation de l'efficacité ne dépendant pas de la dose

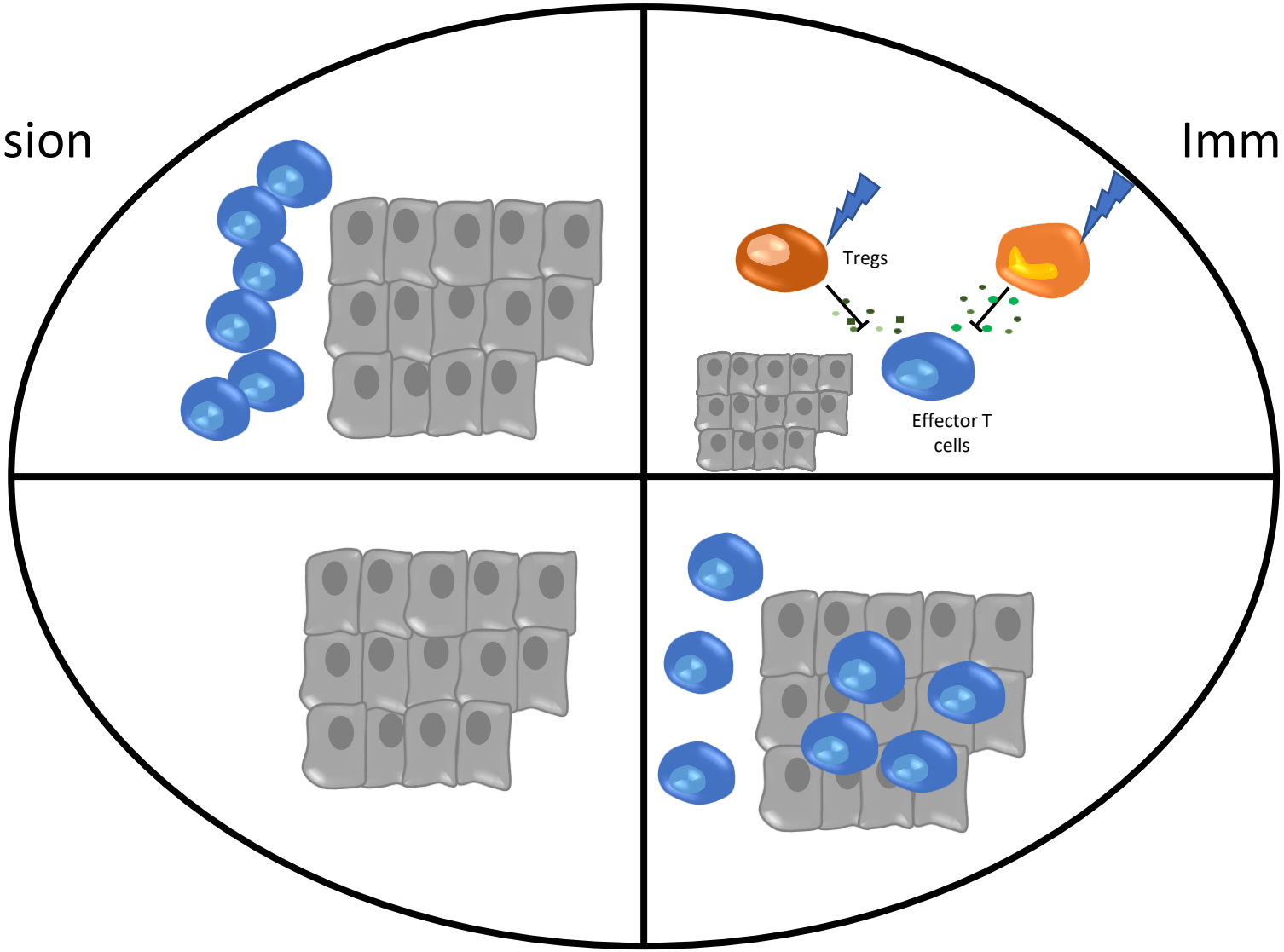


Mishima S Int J Clin Oncol. **25**, 217–239 (2020)

Le contexte immunitaire tumorale

Immuno-exclusion

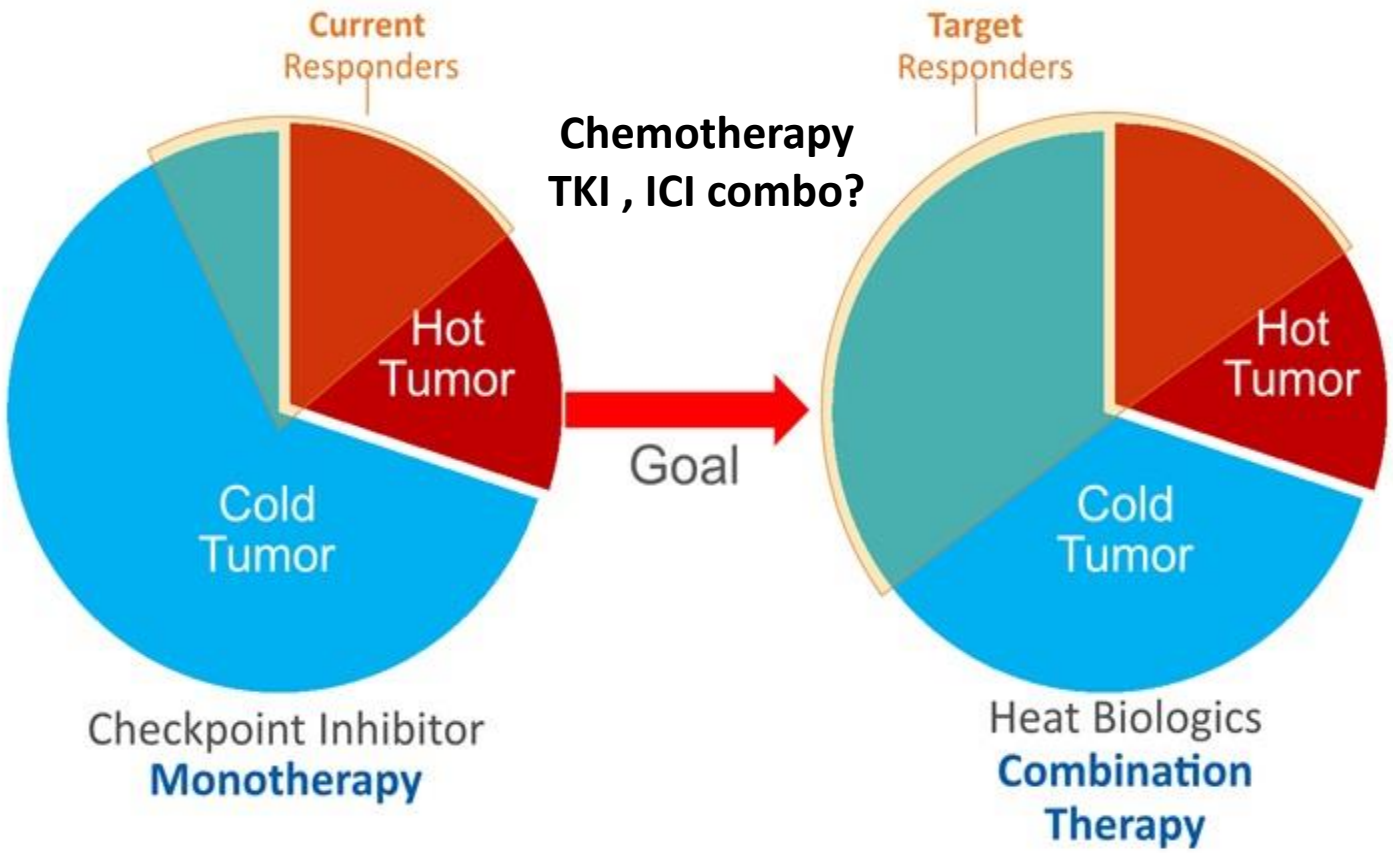
Immunossuppression



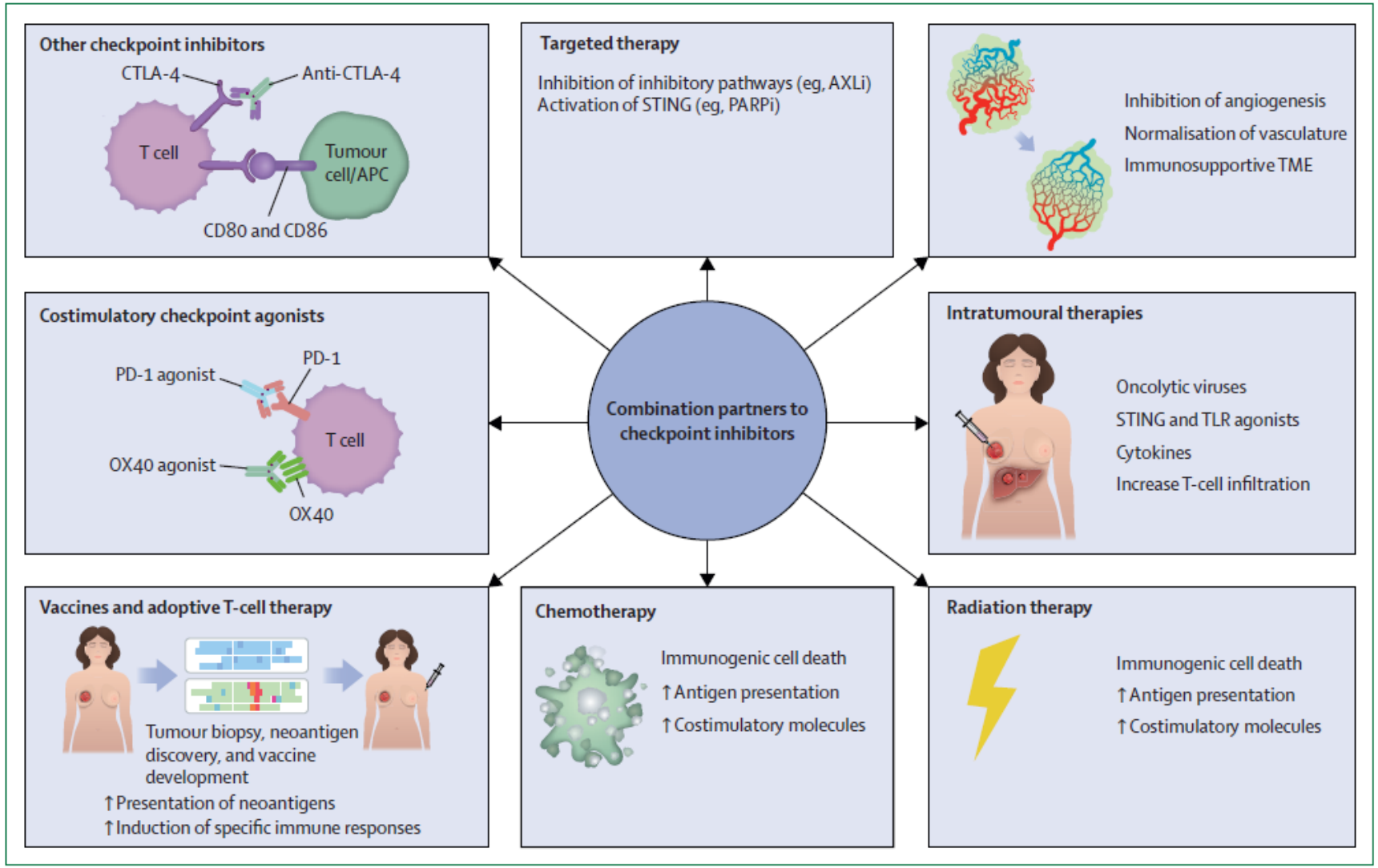
désert

inflammation

Tumor in immune context: switching cold into hot tumors



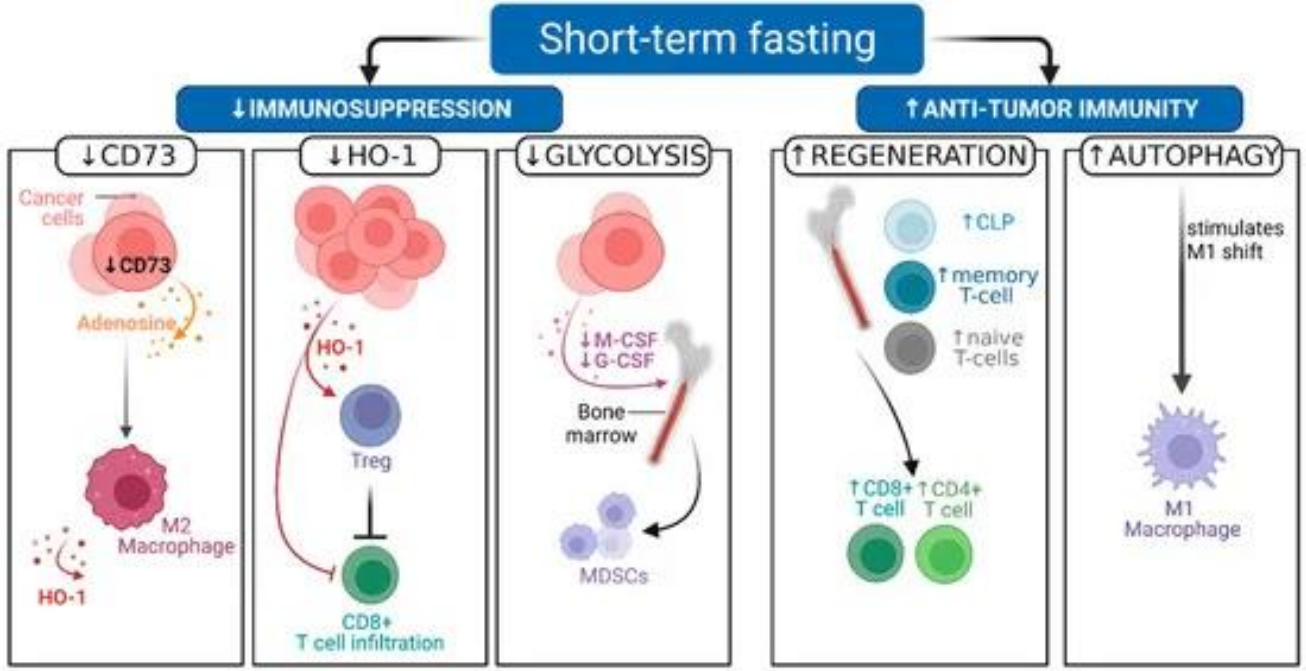
Comment améliorer la réponse immunitaire



ET l'alimentation????

1. Le jeune et la restriction calorique

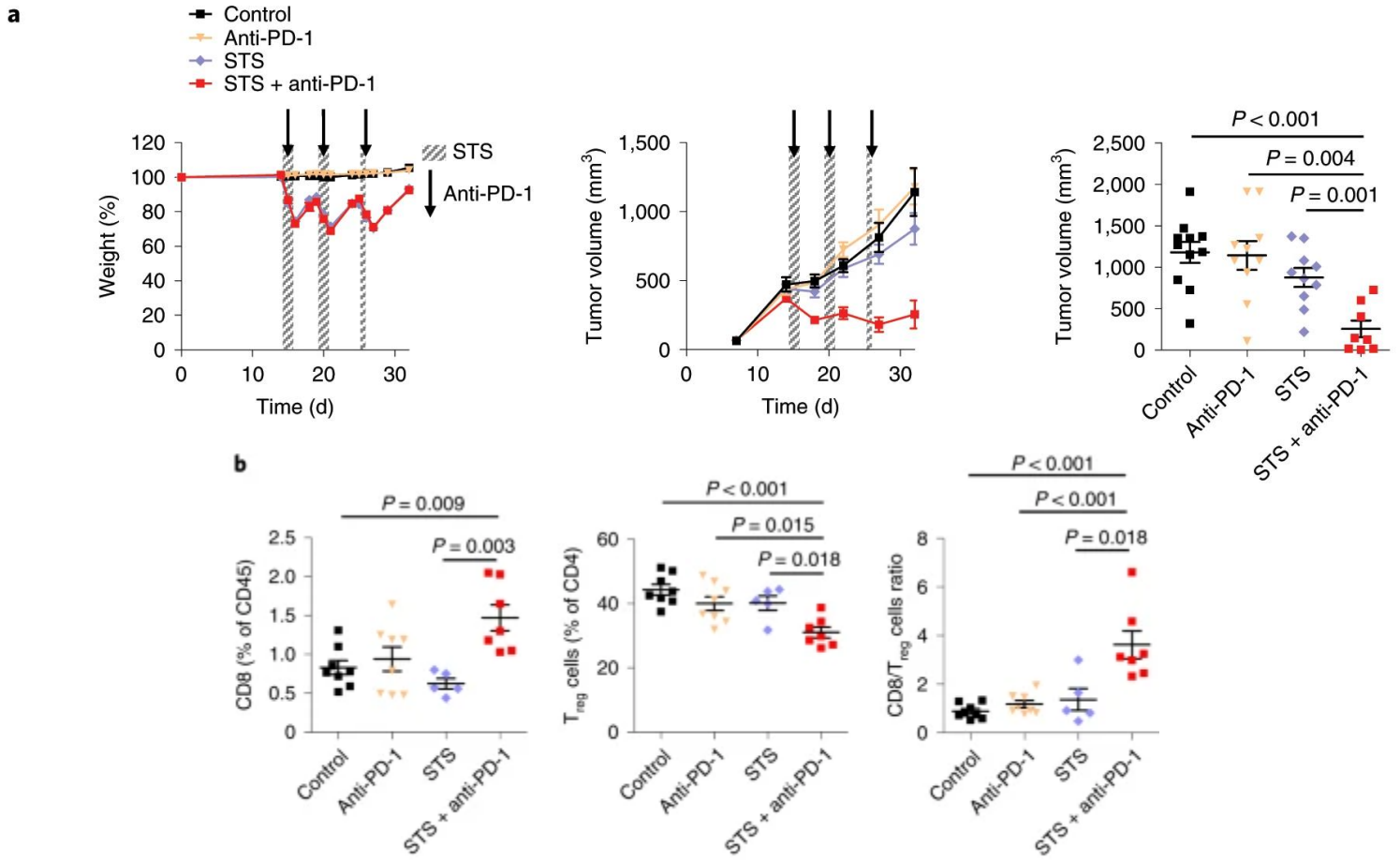
Un effet bénéfique sur la réponse immunitaire



N de Gruil Cancers 2022, 14(6), 1390;

1. Le jeune et la restriction calorique

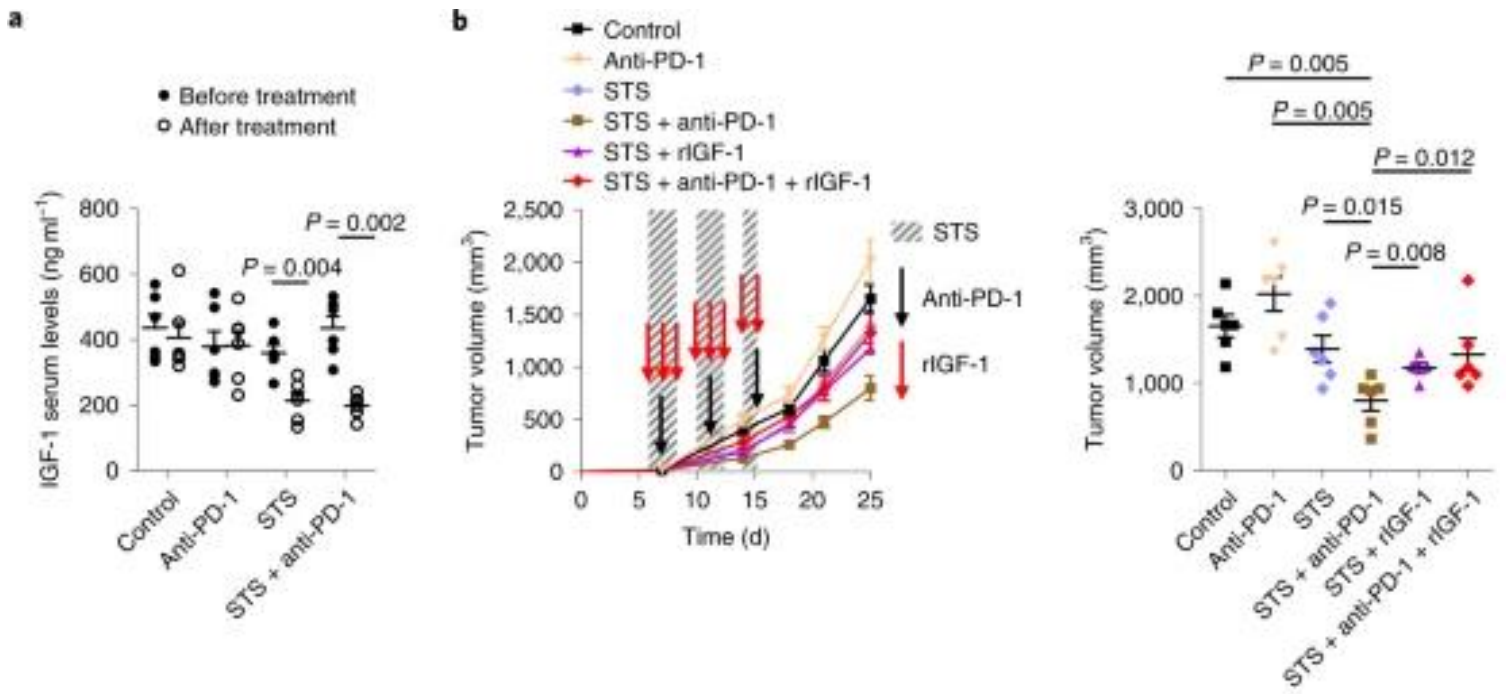
Un effet bénéfique sur la réponse immunitaire augmentation des CD8, diminution des Treg



D Ajona Nature Cancer 1 75–85 (2020)

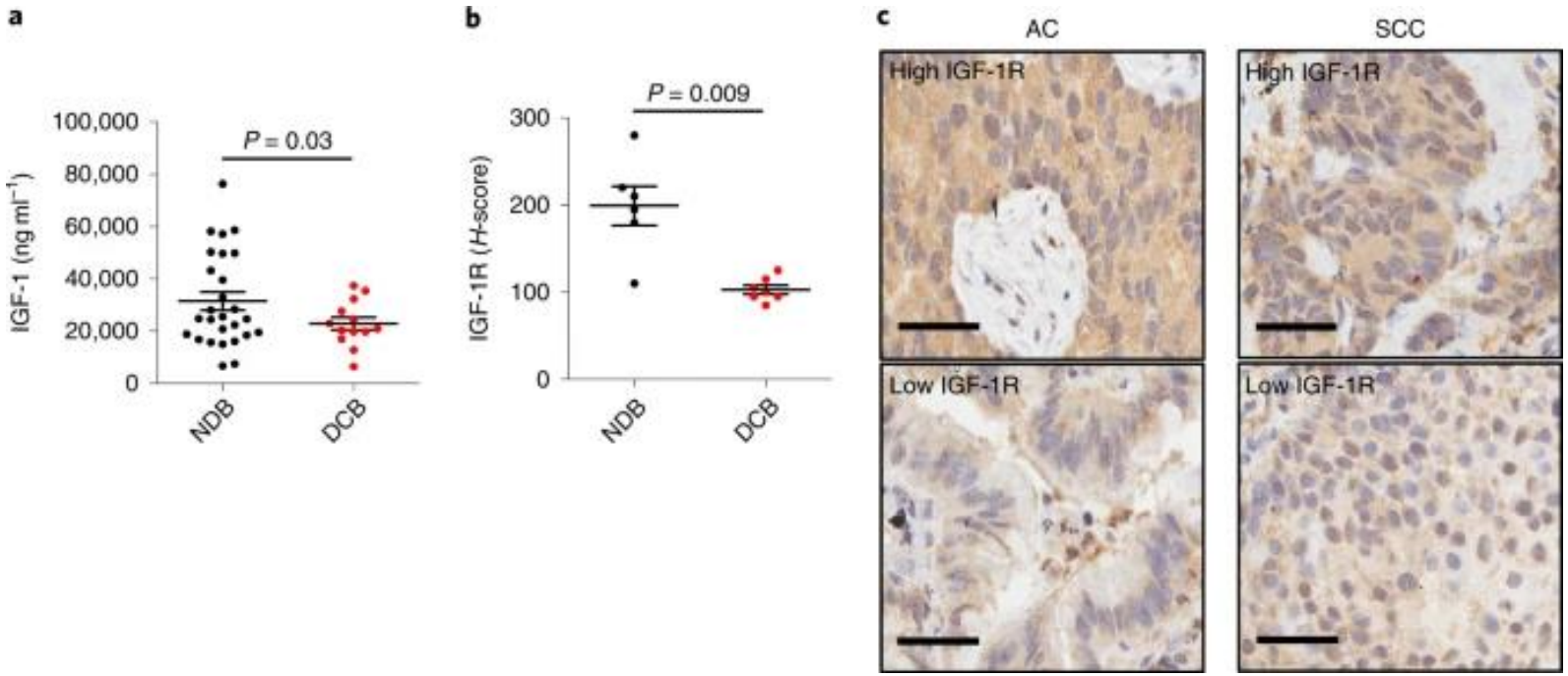
1. Le jeune et la restriction calorique

Un effet bénéfique lié à IGF1



D Ajona Nature Cancer 1 75–85 (2020)

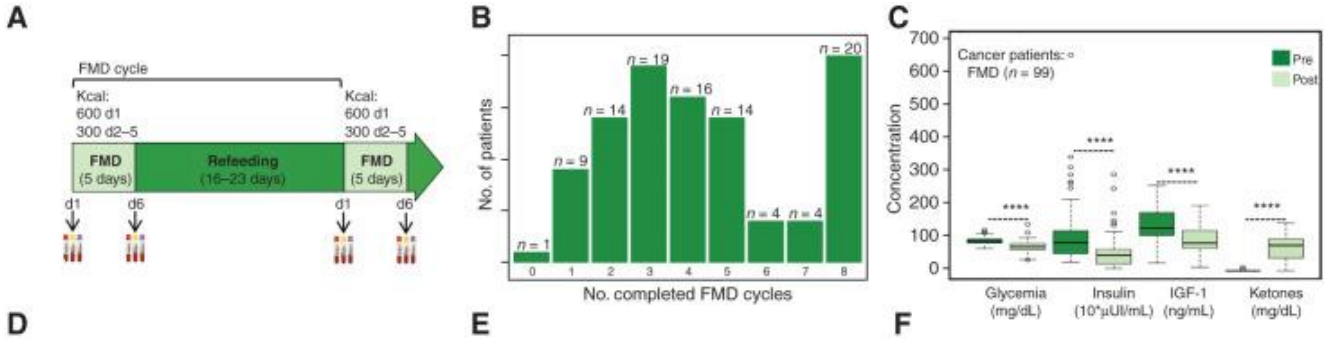
1. Le jeune et la restriction calorique (données cliniques)

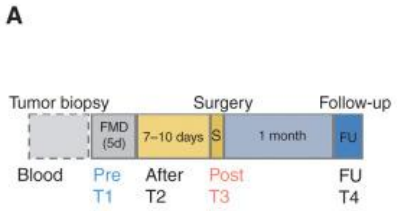


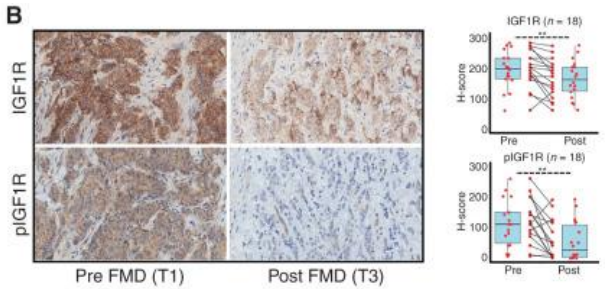
D Ajona Nature Cancer 1 75–85 (2020)

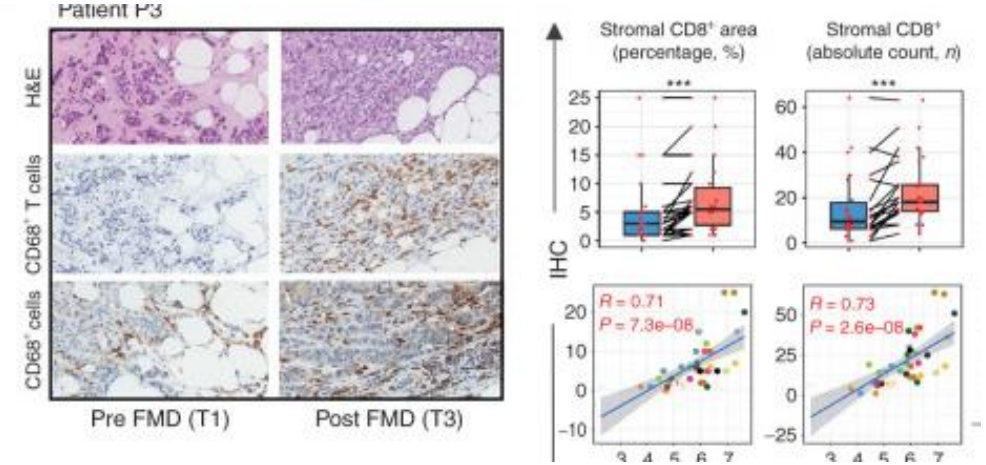
1. Le jeune et la restriction calorique (données cliniques)

Essai thérapeutique









<u>C Vernieri Cancer Discov.</u> 2022 Jan 1; 12(1): 90–107.

1. Le jeune et la restriction calorique (données cliniques)

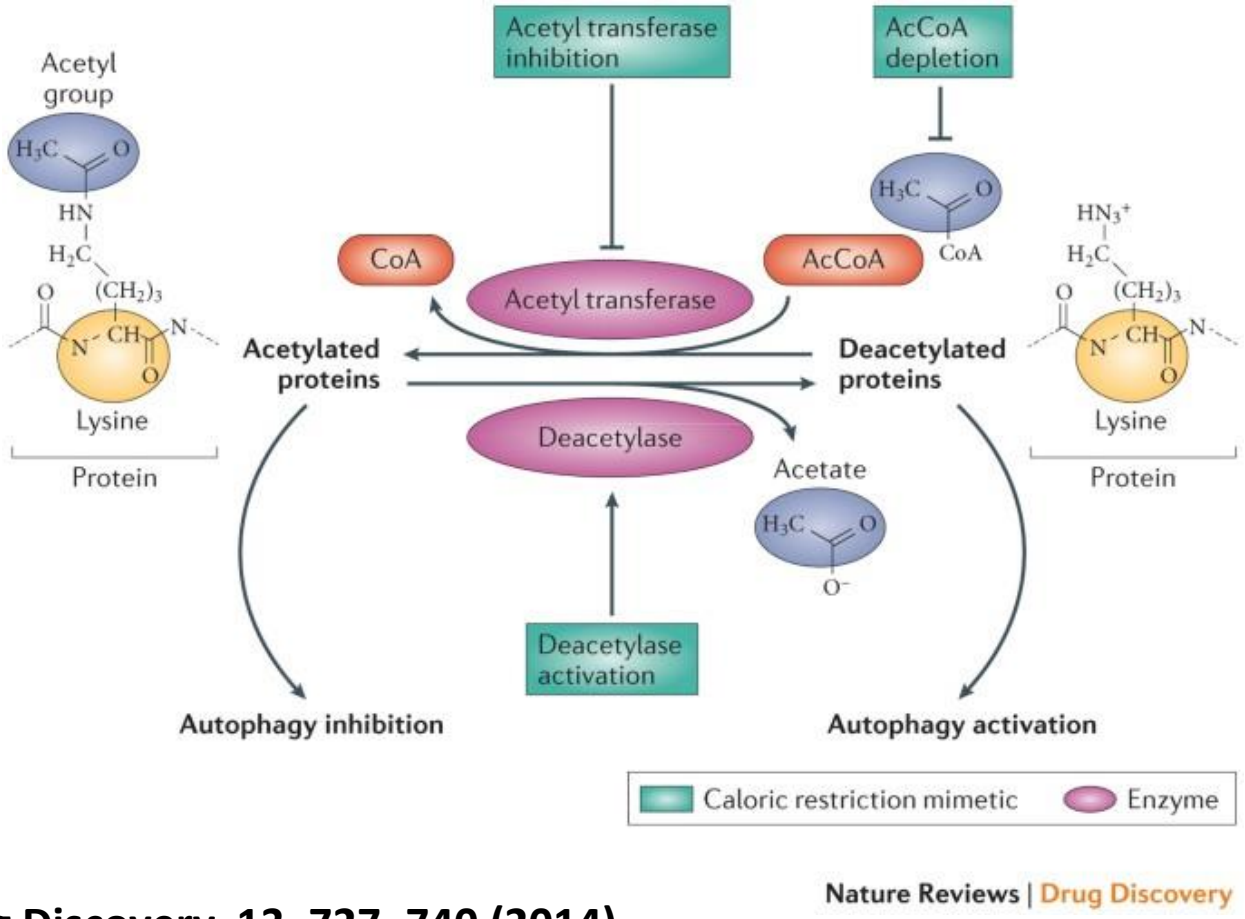
Essai thérapeutique cancer du sein situation neoadjuvante

Restriction calorique 4 jours a chaque cycle

S de Groot. Nat Commun. 2020; 11: 3083.

2. Les mimetiques de la restriction calorique

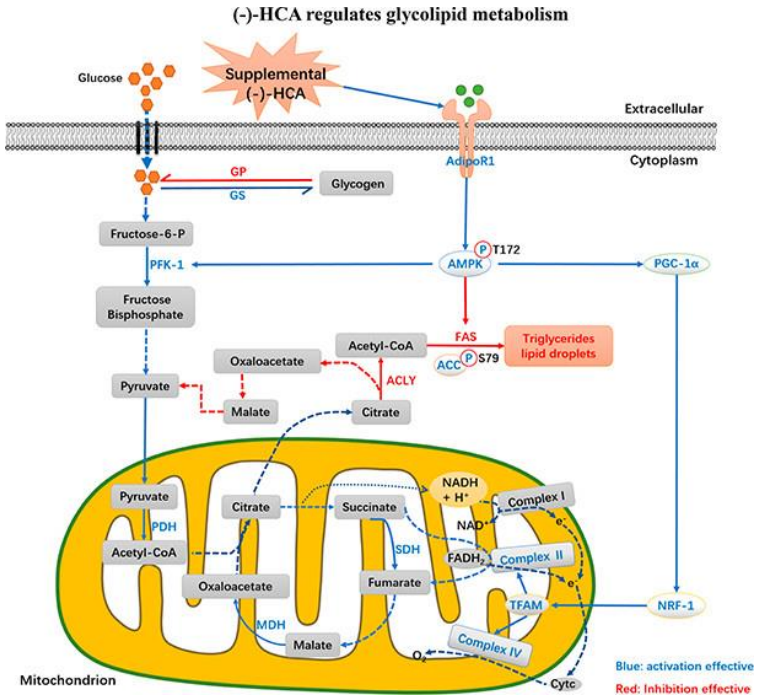
Agents qui stimulant l'autophagie en augmentation la deacetylation des proteines



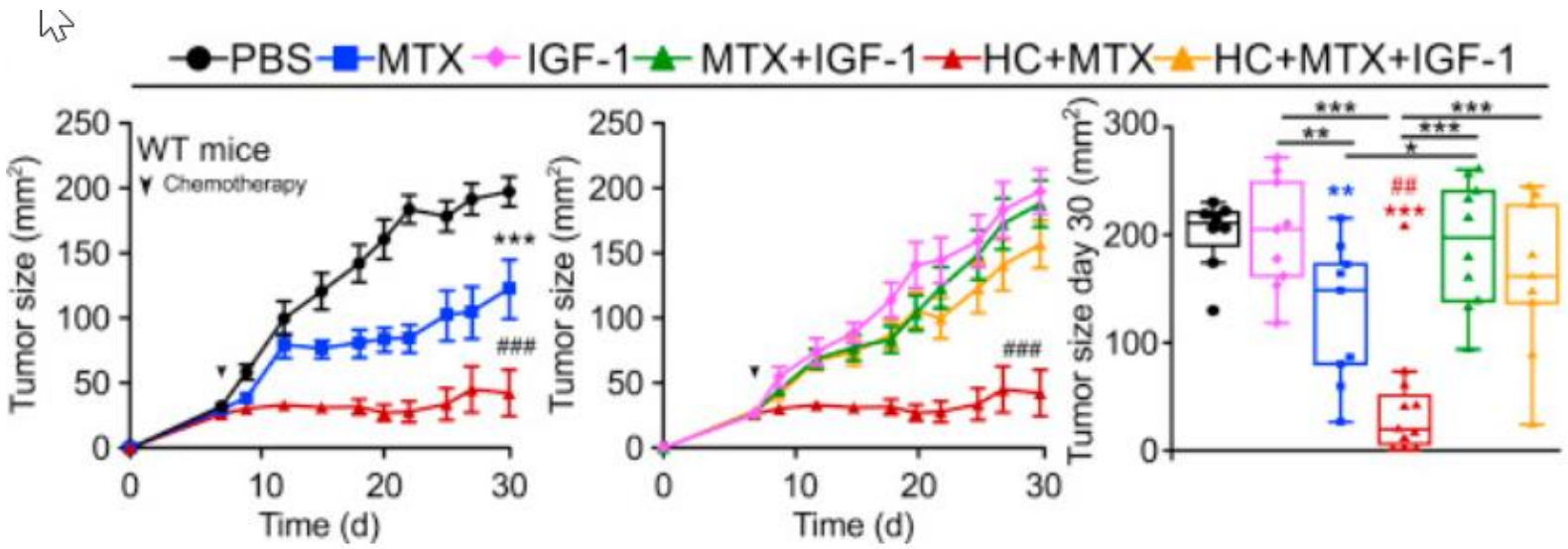
F Madeo Nature Reviews Drug Discovery 13, 727–740 (2014)

2. **Les mimetiques de la restriction calorique**

Agents qui stimulant l'autophagie en augmentation la deacetylation des proteines)= exemple de l'hydroxycitrate



Inhibition mTor, glycolyse et augmentation de la lipolyse



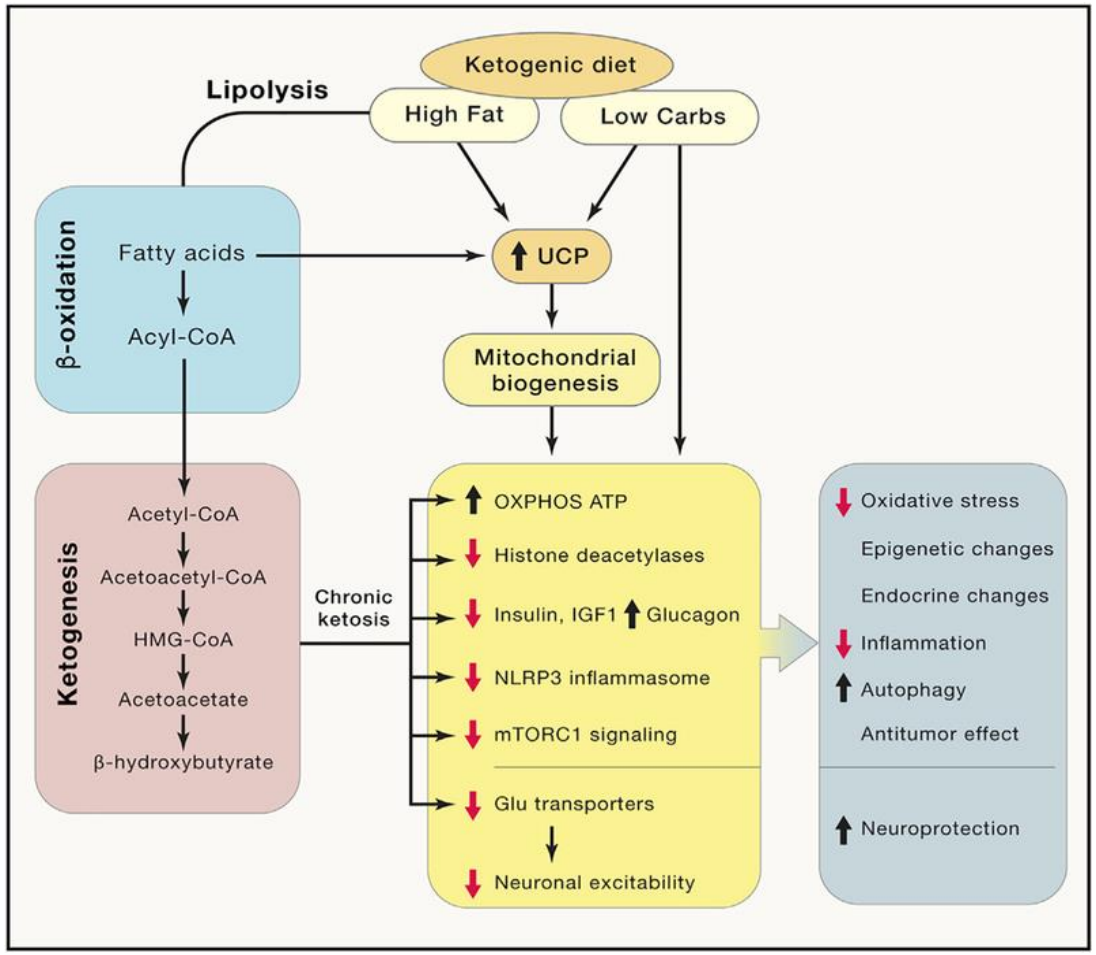
Effet antitumoral dépendant des CD8 et de IGF1

Pietrocola F, Cancer Cell. 2016;30(1):147–160.

3. Les régimes cétogènes:

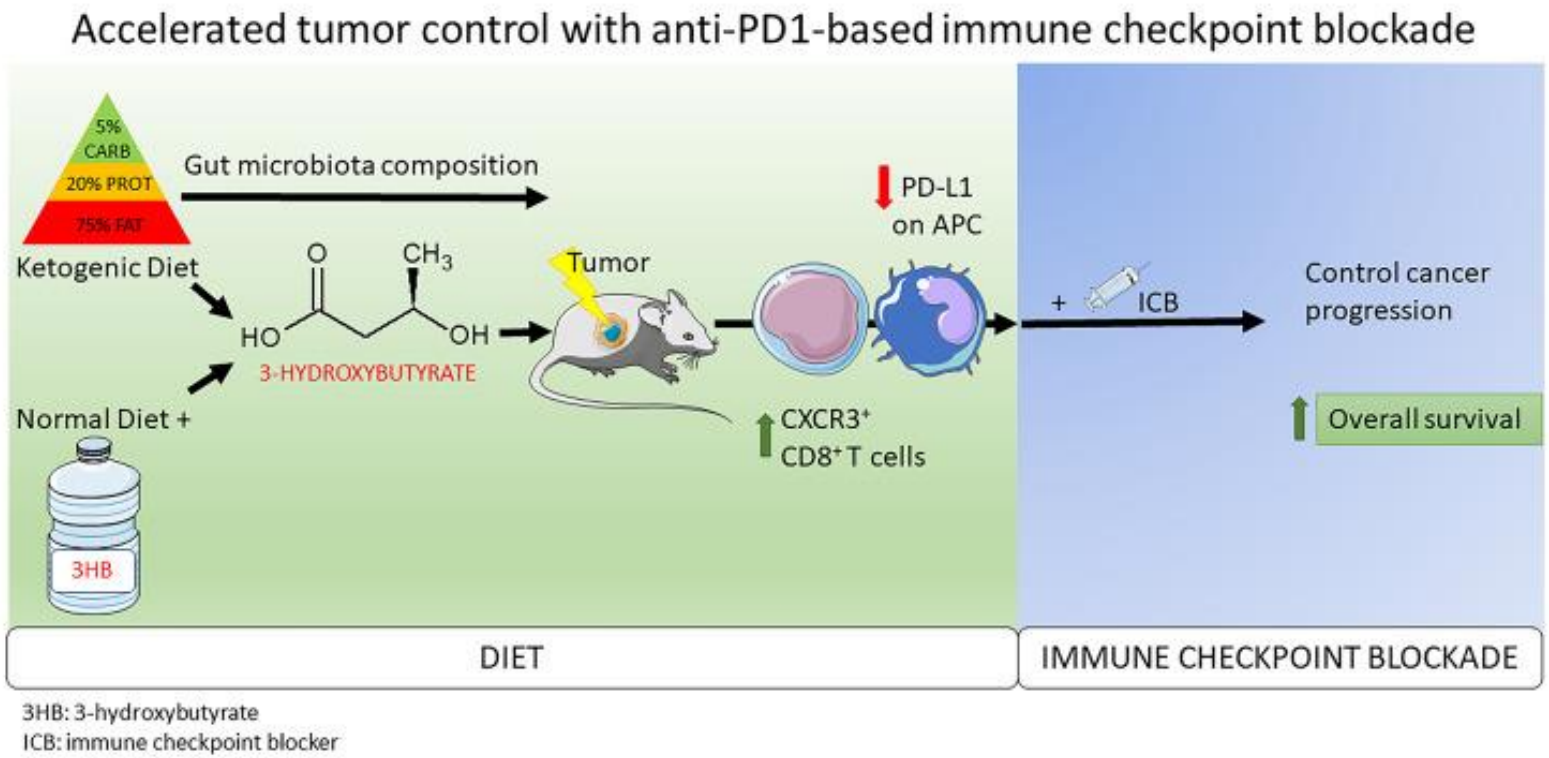
Le regime cétogènes:

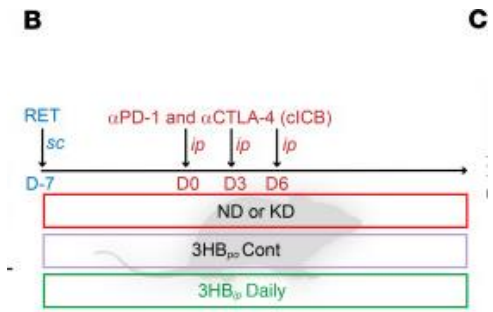
UCP: proteine découplante

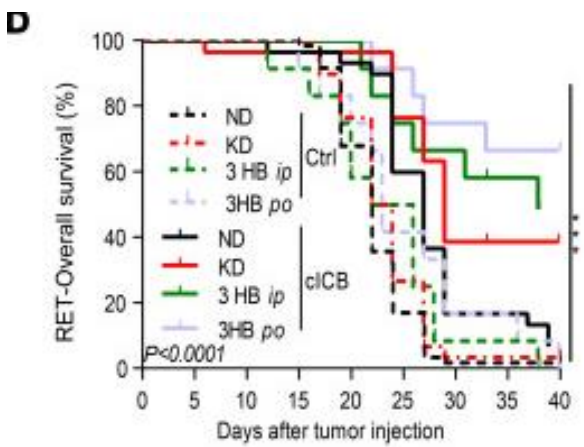


Kroemer G Cell. 2018 Oct 18; 175(3): 605–614.

3. Les régimes cetogènes:

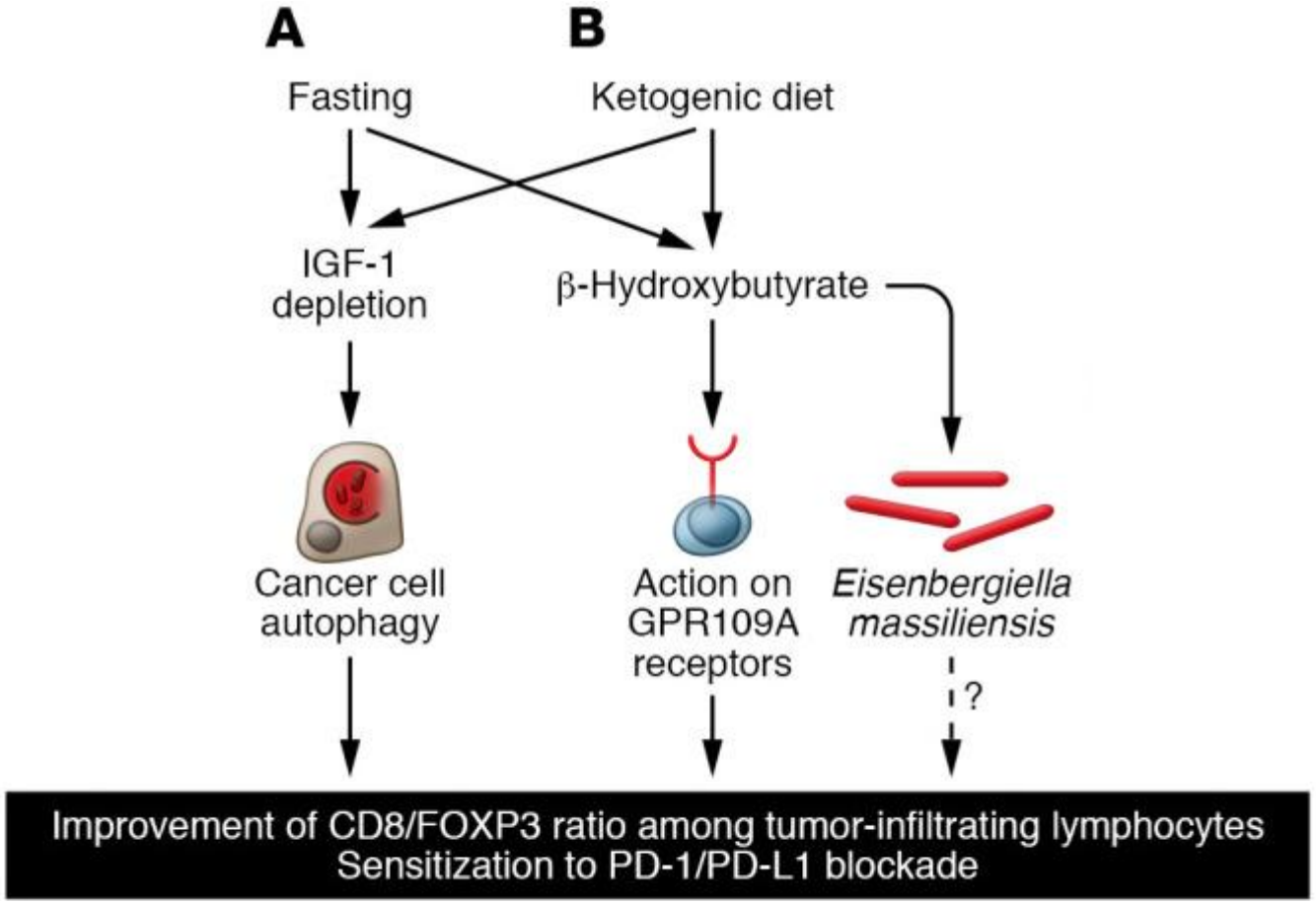






<u>G Ferrere JCI Insight.</u> 2021 Jan 25; 6(2): e145207

En conclusion



Un fort rationnel pour penser que le jeun, la restriction calorique, le regime cetogene augmente l'immunité antitumorale

Nombreux essais cliniques en cours

Conflits of interest

- AstraZeneca, Boehringer Ingelheim, Clovis, GlaxoSmithKline,
  Hoffman la Roche, GSK, Lilly, Pfizer, BMS, MSD, Novartis, Accord Healthcare, Sandoz, Janssen, Takeda, Sanofi, Pierre Fabre et Amgen

Immunothérapies dans le cancer du poumon

- **Cancers non à petites cellules métastatiques**
  - 2ème ligne : nivolumab, atezolizumab (tout PDL1), pembrolizumab si PDL1 > 1%
  - 1ère ligne : pembrolizumab, atezolizumab, cemiplimab si PDL1 > 50%,
  - Pembro Chimio (tout PDL1)
- **Cancers non à petites cellules localement avancées**
  - Durvalumab en consolidation
- **Cancers à petites cellules métastatiques**
  - Atezolizumab en association avec Carbo – VP16
  - Durvalumab en association avec Platin – VP16

Facteurs pouvant influer l'efficacité

- Facteurs cliniques : âge, sexe: F < M?, statut tabagiques, PS, Comorbidities , co médications : corticosteroides, antibiotiques, inhibiteurs de la pompe, antidiabetiques …..
- Facteurs tumorales : histologie, mutations oncolgéniques, PDL1 let TMB
- Facteurs biologiques : rapport neutro/lymphocyte, ….

La prise alimentaire ?

Le cycle nycthéméral ?

Choice of cutoff and choice of endpoint

Cancer Type	Trial Design (No. of Patients)	Intervention	Endpoint	Results	References
Breast	Randomized, multicenter (90)	Time of delivery of vinorelbine	Toxicity	Leukopenia significantly less if maximum delivery at 5:00 P.M.	112
Colorectal	Randomized, multicenter (92)	5-FU + LV 4:00 A.M., oxaliplatin 4:00 P.M. vs. continuous infusion	Toxicity	Severe stomatitis decreased by fivefold with chronotherapy schedule (18 vs. 89%, $P < 0.001$)	110
	Randomized, multicenter (186)			Severe stomatitis decreased by fivefold with chronotherapy schedule (14% vs 76%, $P < 0.0001$)	111
	Randomized, multicenter (92)		Tumor response rate	Response rate significantly higher in chronotherapy schedule (53 vs. 32%, $P < 0.05$)	110
	Randomized, multicenter (186)			Response rate higher in chronotherapy schedule (51 vs. 29%, $P = 0.003$)	111
	Phase III (564)		Survival	Risk of death in men decreased by 25% with chronotherapy (18 vs. 21 mo, $P = 0.02$) Risk of death in women increased by 38% with chronotherapy (19 vs. 16 mo, $P = 0.03$)	118
Endometrial	Phase II (33)	Doxorubicin 6:00 A.M., cisplatin 6:00 P.M.	Toxicity	Well tolerated with 60% response rate	117
	Phase III (342)		Efficacy	No difference in response rate (46% in standard group vs. 49% in chronotherapy group, $P = 0.26$) Decreased leukopenia (75% in standard group, 64% in chronotherapy group; $P < 0.05$), and granulocytopenia (81% in standard group, 74% in chronotherapy group; $P < 0.05$)	113
Lymphoblastic leukemia	Retrospective cohort (118)	6-MP and MTX before 10:00 A.M. vs. after 5:00 P.M.	Disease-free survival	Increased long-term survival for evening group; risk of relapse 2.6 times greater for morning group	114
Pancreas	Phase I (16)	5-FU 4:00 A.M. vs. continuous infusion	Toxicity	Acceptable toxicity at 4:00 A.M.	115
Rectal	Single center, nonrandomized (28)	5-FU administered at 9:00 P.M. × 5 d, with radiation, followed	Toxicity, efficacy	High response rate with minimal toxicity; 7% with grade III toxicities, 52.6% with significant downstaging	116

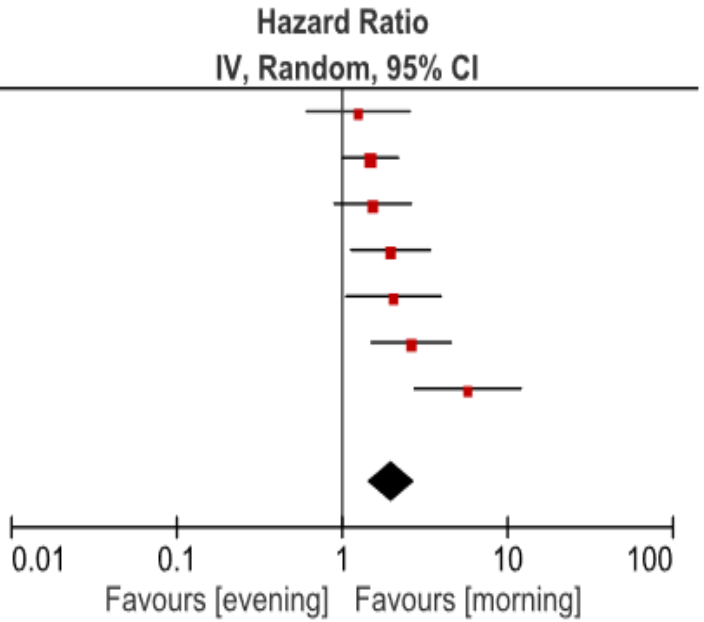
Study Country Method Period	Metastatic cancer	ICI	Infusion cut-off time	Number of patients (M/F)	Outcome measure
Ortego *et al*. [16] Brazil Multicenter, retrospective 2016–2021	Urothelial	Anti-PD-1 Anti-PD-L1	4:30 pm	88 (62/26)	OS PFS
Qian *et al*. [12] USA Longitudinal 2012–2021	Melanoma	Anti-PD-1 Anti-PD-L1 Anti-CTLA-4	4:30 pm	146 (73/73)	OS
Karabouéé *et al*. [13] France Retrospective 2015–2020	NSCLC	Nivolumab	12:54 pm	95 (48/47)	OS PFS
Cortellini *et al*. [14] USA, UK & Italy Multicenter cohort	NSCLC	Pembrolizumab	4:30 pm	180 (136/44)	OS PFS
Barrios *et al*. [19] Spain & Italy Real-world database 2018–2021	NSCLC	Anti-PD-1 Anti-PD-L1	4:00 pm	129 (86/43)	OS PFS
Patel *et al*. [20] USA Retrospective 2015–2020	RCC	Anti-PD-1 Anti-PD-L1 Anti-CTLA-4	1:00 pm	201 (119/82)	OS
Rousseau *et al*. [15] France Retrospective 2014–2021	NSCLC	Nivolumab Pembrolizumab Atezolizumab	4:30 pm	180 (115/65)	OS PFS

Meta analyse sur la survie

Study or Subgroup	Weight	Hazard Ratio IV, Random, 95% CI
Barrios et al	11.5%	1.25 [0.60, 2.60]
Rousseau et al	19.4%	1.48 [0.99, 2.21]
Cortellini et al	15.4%	1.53 [0.88, 2.66]
Patel et al	15.1%	1.96 [1.11, 3.45]
Qian et al	12.7%	2.04 [1.04, 4.00]
Ortego et al	14.9%	2.62 [1.48, 4.64]
Karaboue et al	11.1%	5.74 [2.70, 12.20]
Total (95% CI)	**100.0%**	**2.01 [1.45, 2.78]**

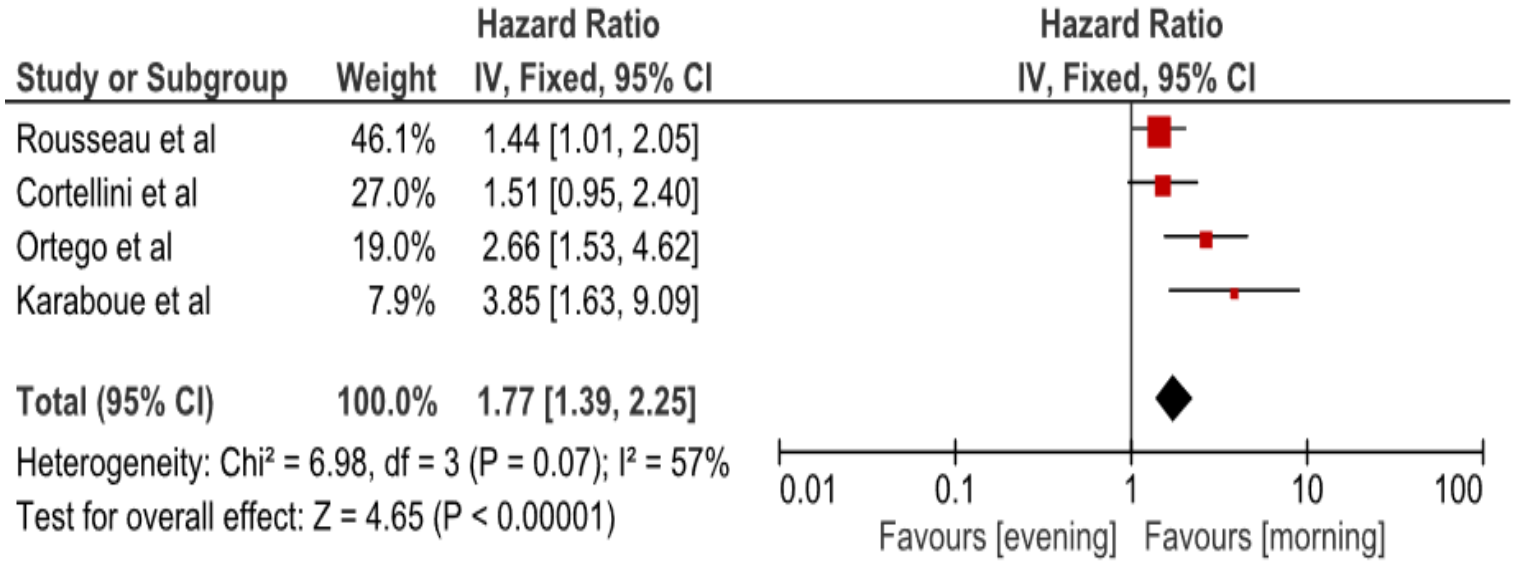
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 12.84$, df = 6 (P = 0.05); $I^2 = 53\%$

Test for overall effect: Z = 4.19 (P < 0.0001)



Etudes pan tumeurs

Meta analyse sur la survie sans progression



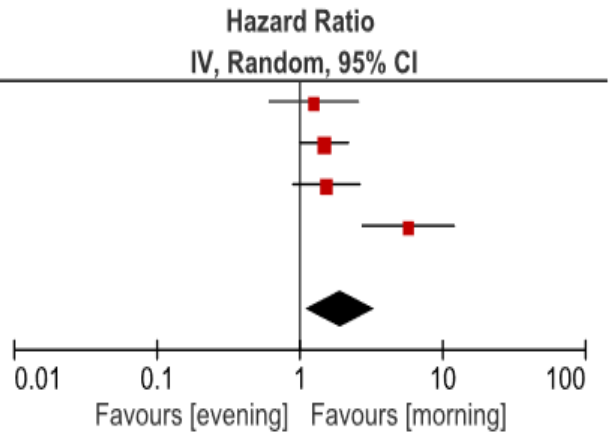
Etudes limités au cancer du poumon

Meta analyse sur la survie

Study or Subgroup	Weight	Hazard Ratio IV, Random, 95% CI
Barrios	22.2%	1.25 [0.60, 2.60]
Rousseau	29.8%	1.48 [0.99, 2.21]
Cortellini	26.3%	1.53 [0.88, 2.66]
Karaboue	21.7%	5.74 [2.70, 12.20]
Total (95% CI)	**100.0%**	**1.93 [1.09, 3.42]**

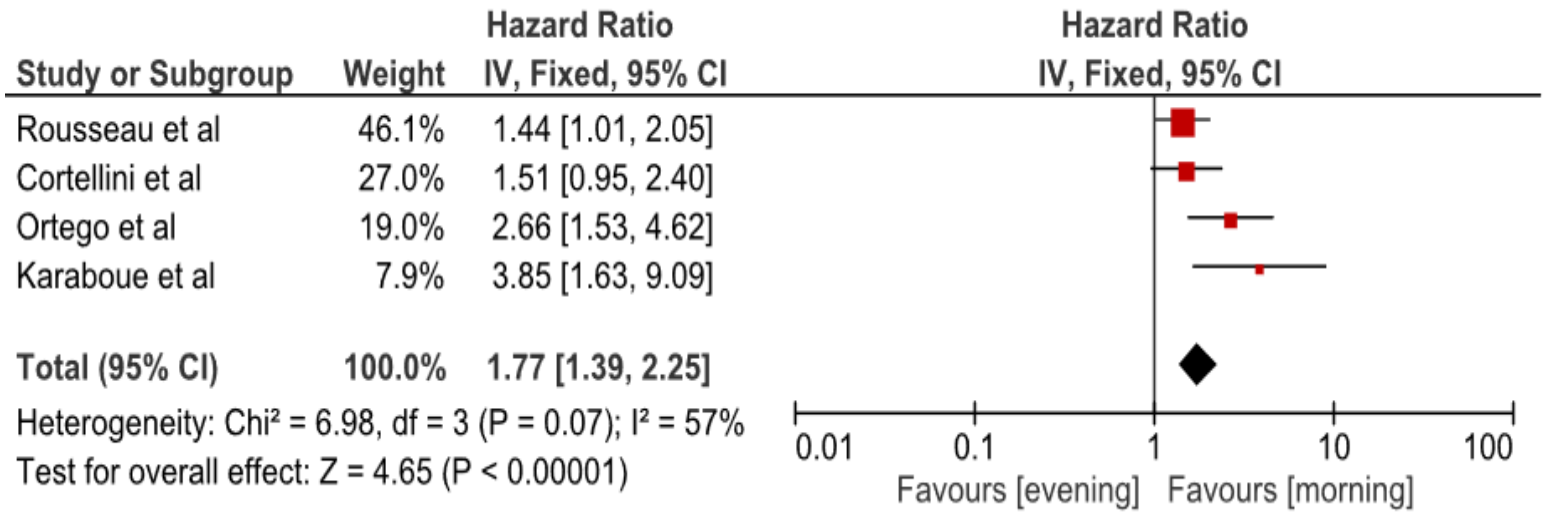
Heterogeneity: Tau² = 0.24; Chi² = 11.23, df = 3 (P = 0.01); I² = 73%

Test for overall effect: Z = 2.26 (P = 0.02)



Etudes n’ayant inclus que des cancers du poumon

Meta analyse sur la survie sans progression



Etudes n’ayant inclus que des cancers du poumon

IMMUNOTIME (project, Ducheman B, Levi F)

- Evaluation of the effect of time of administration on the activity of pembrolizumab monotherapy in metastatic non-small cell lung cancer (PDL> 50%)
- A randomized multicenter phase III trial
- Morning (9:00 – 14:00) vs afternoon (14:00 - 17:00)
- Primary outcome : 2-years-PFS

Conclusions

- Etudes rétrospectives
- Facteurs confondants
- Demi vie longue
- Horloge interne / horloga par organe/ horloge de la maladie

- Utiliser els données de vraie vie et els outils de l'IA pour mieux comprendre les enjeux du moment de l'administration